Claim 1 has been cancelled without prejudice, and claim 2 has been amended to more particularly define the present invention. Further, claims 3-5, 8, 12 and 13 have been amended to depend on claim 2, and claims 12 and 13 have been amended to specifically recite R^{10} to R^{14} from claim 9 since claim 9 is a non-elected claim. Support for the claim amendments is readily apparent from the teachings of the specification and the original claims.

With regard to the rejection of claims 1-7, 12 and 13 under 35 USC § 112, first paragraph, this rejection is deemed to be untenable in view of the claim amendments and the following remarks, and is thus respectfully traversed.

Applicants have provided additional biological data which are enclosed herewith (Appendix 2, Tables A and B). These data have been obtained according to the methods disclosed in the specification.

Applicants believe that the substituents as set forth in claim 2 are well supported by the disclosures in the specification, including Preparation Examples 1 to 107, Biological Examples 1 to 5 (Tables 1 to 4) and pages 27-75 of the specification, as well as the data in Appendix 2.

As compared with U.S. Patents 5,665,753 and 5,691,381, enclosed herewith, in which the *most* of the specie compounds of the claimed genus are not tested for activity (see column 17, lines 62-63, of USP 5,665,753 and column 34, lines 61-62, of USP 5,691,381), the teachings of the specification, and the Examples contained therein

and enclosed herewith clearly provide representative support for the claims under 35 USC § 112, first paragraph.

As stated in § 2164.01 of the Manual of Patent Examining Procedure (MPEP), the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)*. In reviewing and comparing the examples of the enclosed Patents with that of the present specification, it is clear that the experimention needed to practice the claimed invention is not undue. The working examples of the specification are clearly representative of the claimed genus and thus, support the species which have not been specifically tested for function and efficacy.

As stated in § 2164.02 of the MPEP, for a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.

It is also important to note that in *In re Angstadt 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976)* (a case in which the facts are analogous to the present application), the court held that not every species encompassed by the claims, <u>even in unpredictable arts</u>, need

to be tested and disclosed. The court observed that if § 112 required a disclosure of a test with every species covered by a claim in an unpredictable art, then a prohibitive number of actual experiments would have to be performed, discouraging the filing of patent applications in unpredictable areas. *Id. at 502-03, 190 U.S.P.Q.2d at 218.*

Thus, given that the disclosure in the specification teaches one skilled in the arts how to practice the claimed invention without undue experimentation as shown in Appendix 2 enclosed herewith, this rejection can no longer be sustained and should be withdrawn.

With regard to the rejection of claims 1-7, 12 and 13 under 35 USC § 102(b) as being anticipated by Dickens et al. (WO 94/02447), this rejection is deemed to be untenable in view of the amended claims, and is thus respectfully traversed.

To constitute anticipation of the claimed invention, a single prior art reference must disclose each and every material element of the claim. Here, in this case, the compound in Dickens et al. noted by the Examiner, does not anticipate or render obvious the newly amended claims.

Specifically, the Examiner argues that Dickens et al. teach a compound with the structure shown in Example 6 (see page 24, Example 6 of the reference) which anticipates the claimed invention. The Examiner believes that this compound of Dickens et al. anticipates the compound of formula I, claim 1, since it comprises a situation wherein R^1 and R^2 are hydrogen, R^3 is hydroxy, R^4 is a butyl group, R^5

is hydrogen and R^6 is methyl, R^7 and R^8 are hydrogen, and R^9 is a form of a substituted alkylene. The Examiner further believes that Dickens et al. further teach that R^5 can be a lower alkyl (as required by claims 2, 3, 12 and 13 of the present application), while all other elements can be the same. The Examiner also observes that the Dickens et al. compound R^9 is a ring, but has an amino group and an unsaturated alkyl chain within the group, which the Examiner believes, meets the requirements of claim 3.

However, Applicants respectfully disagree with the Examiner's conclusions in this regard. In Example 6 of Dickens et al., WO 94/02447, *R^9 is 1-pyrazolyl but not a substituted alkylene*. The group for R^9 as set forth in the present invention *does not include a pyrazolyl group*. In addition, R^3 is always hydroxy in Dickens et al., while R^3 does not include hydroxy in the present invention as a result of the current amendment to the claims.

As well understood by one skilled in the art based on the teachings of the specification, the moiety $-CH(R^7)(R^8)(R^9)$ means that the presently claimed compounds of formula I are water-soluble. In other words, the presently claimed compounds of formula I exert a good water-solubility and have the property of being well absorbed by oral routes.

Specifically, water-soluble substituents are selected for R^9 of the compounds according to the present invention, leading to unique compounds each having not only an improved water-solubility but also the unexpected property of being well absorbed by oral routes.

Further, as disclosed and shown in the specification and Examples, the claim compounds exert an excellent inhibitory activity against MMP-1, MMP-3, etc. and inhibit excellently the production of TNF-α as shown in Tables 1 to 3 (see pages 148-152 of the specification). Further, the claimed compounds are advantageously well absorbed by oral routes, as compared with the prior art compounds, see, for example, Reference Compound No. 2 (corresponding to Example 10 of Dickens et al., WO 94/02447), as shown in Table 4 of the specification (see page 154 of the specification).

Lastly, the claimed compounds are non-toxic and thus, would be safe in pharmaceutical applications. In toxicity evaluation experiments, the presently claimed compounds were administered to animals and found to neither kill nor reduce the animals' body weight.

Thus, since the presently claimed compounds are clearly distinct from the prior art compounds in both biological activity and chemical structure, this rejection can no longer be sustained and should be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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